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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,506	08/06/2001	Marta Blumenfeld	50.US3.PCT	9451

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,506	BLUMENFELD ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/8/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-5,8,11,13-15,19,23-25,28,35-37,39,47,48,51 and 57* is/are pending in the application.

4a) Of the above claim(s) *1-5,8,11,13-15,19,23-25,51 and 57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,35-37,39,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0303* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed May 7, 2003. Currently, claims 1-5, 8, 11, 13-15, 19, 23-25, 28, 35-37, 39, 47, 48, 51, 57 are pending. Claims 1-5, 8, 11, 13-15, 19, 23-25, 51, 57 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group III (Claims 28, 35-37, 39, 47, 48) in Paper filed May 7, 2003 is acknowledged.

Claims 1-5, 8, 11, 13-15, 19, 23-25, 51, 57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This BIB data sheet and 371 papers of this application claims priority to provisional applications 60/103,955 and 60/106,457, however, neither the oath, the first line of the specification, nor the ADS sheet refers to these provisional applications. Therefore, it is presumed that no priority has been claims. Clarification is requested.

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the

list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

5. The drawings are acceptable.

Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

It is noted that sequences have been included in the instant specification which are not identified by SEQ ID NO:. For example, pages 147, 157 contain sequences which lack an identifier.

Specification

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

On page 24, for example, reference to a website is present.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 28, 35-37, 39, 47, 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In so far as the claimed invention requires a diagnostic method for determining whether an individual is at risk of developing schizophrenia, the instant specification fails to provide a predictable association between A15 and schizophrenia. Moreover, the claims fail to meet the enablement criteria because the specification fails to teach the skilled artisan how to use the broadly claimed invention.

The specification defines the G713 gene as located on chromosome 13 at locus 13q33. The speciation teaches that previous results of linkage studies have shown that chromosome 13 is likely to harbor a schizophrenia susceptibility locus on 13q32. The specification states that the term G713-related biallelic marker and 13q31-q33-realted biallelic marker relates to a set of biallelic markers either in linkage disequilibrium with the G713 gene or biallelic markers residing in the human chromosome 13q31-q33 region (page 15).

The specification teaches that "trait" refers to any visible, detectable or otherwise measurable property of an organism such as symptoms of, or susceptibility to a disease. A trait can be, without to be limited to, cancers, developmental disease, and neurological disease (page 16).

The specification has taught 11 biallelic markers within G713 region (Page 50). Moreover, the specification has taught 34 biallelic markers within the 13q31-q33-related region (page 50). The specification teaches that G713 genomic sequence is illustrated in SEQ ID NO: 1 to 3. The specification teaches the G713 cDNA sequence is illustrated in SEQ ID NO: 6 or 11. SEQ ID NO: 1 is 5,222 nucleotides in length. SEQ ID NO: 2 is 21, 278 nucleotides in length. SEQ ID NO: 3 is 21,636 nucleotides in length. SEQ ID NO: 6 is 1,791 nucleotides and SEQ ID NO: 11 is 25 nucleotides. Moreover, the specification provides numerous tables depicting analysis performed on various haplotypes comprising two, three or four markers. The specification is silent with respect to any particular analysis on individual markers. As seen in Table 14 directed to cases of schizophrenia with no family history, marker A15 (99-15664/185) is present in haplotypes which are not associated with a statistical significance. In fact, none of the haplotypes appear to confer any level of significance. Studying Table 15, directed to cases with family history, several haplotypes exhibited statistical significance. However, the presence of a T at position A15 does not appear to be the causative factor since haplotype 1, containing a T is significantly associated where as haplotypes 5, 6, 10 are not significant. Therefore, based upon the Tables, it does not appear that A15 provides enough information to obtain a significant result alone.

The art teaches a high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32. Detera-Wadleigh (PNAS, Vol. 96, pages 5604-5609, May 1999) teaches the strongest evidence for linkage is centered at chromosome 13q32 which yielded a lod score of > 3 (page 5605, col. 2).

Ulbrecht et al. (Am. J. Respir. Crit Care Med. Vol. 161, pages 469-474, 2000) teaches genotyping individuals for three single nucleotide polymorphisms of the beta2-adrenoreceptor gene. Ulbrecht concludes that "whereas no individual polymoprhism was associated with bronchial hyperresponsiveness (BHR), the Gly16/Glyn27/Th164 haplotype was significantly underrepresented in the case group indicating a protective effect of this haplotype with regard to BHR."

Neither the specification or the art teach the skilled artisan how to use the invention as broadly as claimed. The specification and the claims of the instant application assert that detection of a biallelic maker allows for detection of an association. While one could conduct additional experimentation to determine whether newly identified biallelic makers might be associated with the wide genus of "traits", the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. With regard to Claims 28, 35-37, 39, the claims are only enabled to the extent that they are directed to the specific biallelic markers taught in the instant specification and schizophrenia cases with family history. The specification has only asserted how to use the information obtained from analysis directed to associations with schizophrenia. The specification has not taught any direction how to determine how to use the information in the event that the biallelic

maker were to be associated with sex, hair color, eye color, height, cancers, diabetes, weight, etc (all examples of traits). It is unpredictable that any association of the markers would exist with any particular traits. The art teach the linkage of the region to schizophrenia, but fails to discuss the linkage of the region with any particular traits. It is unpredictable whether any quantity of experimentation would allow one to practice the claimed invention.

With specific regard to claims 47-48 directed to schizophrenia and A15 marker, the tables appear to illustrate that A15 is not associated alone with schizophrenia. In absence of guidance from the specification, the A15 marker has not been analyzed alone for associations with schizophrenia. As taught by the art, the presence of particular haplotype associations does not infer that individual polymorphisms are associated with the traits. Therefore, absent specific analysis for the particular markers, it is unpredictable whether the individual makers are associated with schizophrenia.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 28, 35-37, 39, 47, 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to detecting nucleotide at a G713 or 13q31-q33-related biallelic marker.

The specification defines the G713 gene as located on chromosome 13 at locus 13q33. The speciation teaches that previous results of linkage studies have shown that chromosome 13 is likely to harbor a schizophrenia susceptibility locus on 13q32. The specification states that the term G713-related biallelic marker and 13q31-q33-realted biallelic marker relates to a set of biallelic markers either in linkage disequilibrium with the G713 gene or biallelic markers residing in the human chromosome 13q31-q33 region (page 15).

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The specification teaches that G713 genomic sequence is illustrated in SEQ ID NO: 1 to 3. The specification teaches the G713 cDNA sequence is illustrated in SEQ ID NO: 6 or 11. SEQ ID NO: 1 is 5,222 nucleotides in length. SEQ ID NO: 2 is 21, 278 nucleotides in length. SEQ ID NO: 3 is 21,636 nucleotides in length. SEQ ID NO: 6 is 1,791 nucleotides and SEQ ID NO: 11 is 25 nucleotides.

The art teaches that the most common variations are single nucleotide polymorphisms (SNPs) which occur approximately once every 100-300 bases (www.ncbi.nlm.nih.gov/SNP/).

Based upon the attachment of SEQ ID NO: 1-3, the genomic sequence is over 49,000 nucleotides in length. The specification has described only 11 markers within the G713 region. The specification teaches only 11 alleles within the scope of the genus: of G713. The specification proposes to discover other members of the genus by using a hybridization or microsequencing or other well known methods (page 55-59). Given the teachings in the art, regarding the frequency of SNPs, one would reasonably expect 163-490 SNPs within a 49,000 base pair region. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of G713 relates to the structure of different alleles. In addition, according to the standard definition, the genus includes members that would be expected to have widely divergent functional properties. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of other unknown alleles having concordant or discordant functions. The common attributes of the genus are not described and the identifying attributes of the individual alleles, other than the 11 specific biallelic markers taught, are not described. The nature of alleles is that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others. According to these facts, one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only 11 members of this genus is not representative of the

variants of the genus and is insufficient to support the claim. Similarly, the disclosure of 34 biallelic markers within the extremely large chromosomal region of 13q31-q33 has not been described for the forgoing rationale.

Moreover, there is not adequate description of the genus of variants in disequilibrium with the disclosed biallelic markers. The specification fails to disclose any biallelic makers which are "related" or in "linkage disequilibrium" within the scope of the genus. The general knowledge in the art concerning variants in linkage disequilibrium does not provide any indication of how to readily identify these variants. There is substantial variability among the species of nucleic acids encompassed in the scope of the claim because only 11 specific mutations have been identified in the gene with three exons which spans more than 45,000 nucleotides. The specification has also not defined a structural feature of the variants which would be common to all members of the genus that constitutes a substantial portion of the genus. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "G713 or 13q31-q33 related biallelic markers" because the description of only 11 members of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the specification does not adequately provide a written description for G713 or 13q31-q33 related biallelic markers.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 28, 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Smulson et al. (US Pat. 5,449,605, September 12, 1995).

Smulson et al. (herein referred to as Smulson) teaches a method of detecting a predisposition to cancer by detecting a deletion polymorphism in the gene for human poly polymerase. The method of Smulson uses a hybridization probe which will identify a restriction fragment length polymorphism within the 13q33-qter locus (abstract). Smulson teaches that the polymorphism may be detected using a hybridization probe or allele specific amplification primers which are capable of distinguishing between the A and B allele (col. 3, lines 55-60). Smulson teaches that the initial study of DNA derived from tumor and normal tissue of the same individiual was examined. Analysis was also performed for noncancer populations which showed a marked difference in the frequency of the B allele (col. 3, lines 20-25). As seen in Figure 10, genotypes are evaluated using a southern blot. Therefore, it is evident that since a marked difference was seen in tumor DNA, Smulson determined the frequency in both a positive and control population and determined whether an association exists. Therefore, Smulson anticipates each element of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 28, 35-37, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swift et al (US Pat. 5,464,742, November 7, 1995) in view of Detera-Wadleigh et al (PNAS, Vol. 96, pages 5604-5609, May 1999).

Swift et al. teaches assessing association of an allele and a disease by determining the allele frequency in a population of patients with a disease, determining the frequency of an allele in a population of control patients and determining whether the frequency of the allele in the disease population is statistically significant. These steps are the only steps required by the claims.

Swift does not specifically teach analyzing the 13q31-q33 region for genotypes and trait associations.

However, Detera-Wadleigh teaches a high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32. Detera-Wadleigh teaches the strongest evidence for linkage is centered at chromosome 13q32 which yielded a lod score of > 3 (page 5605, col..2).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have screened 13q32 for alleles which differed between individuals and determined whether an association existed between the alleles and traits. The art teaches that the 13q32 region is strongly linked to affective disorder and schizophrenia series and is conceivably the predisposing fact for psychoses. Given the strong linkage analysis, the skilled artisan would analyze the known linked region for

alleles and determine whether an association between the alleles and psychoses is present. At the time of filing, it was well within the scope of the ordinary artisan to perform methods to test for association of an allele and a disease as exemplified by Swift. Moreover, Detera-Wadleigh specifically teaches the 13q32 region is linked to psychoses disorders. Therefore, given the general suggestion by Swift to perform population-based tests of gene-disease associations, the ordinary artisan would have been motivated to have analyzed a known linked region for associations with traits.

12. Claims 28, 35-37, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Swift et al (US Pat. 5,464,742, November 7, 1995).

Swift et al. teaches assessing association of an allele and a disease by determining the allele frequency in a population of patients with a disease, determining the frequency of an allele in a population of control patients and determining whether the frequency of the allele in the disease population is statistically significant. These steps are the only steps required by the claims.

The difference between the prior art and the claimed invention is the recited G713 or 13q31-q33-related biallelic information. This information is descriptive information. This information is fed into a known method whose purpose is to compare or modify those data using a series of processing steps that do not impose a change in the processing steps and are thus nonfunctional descriptive material. The claimed invention uses known analysis methods to solve a known problem in a conventional manner. The instant specification acknowledges known prior art association techniques

(page 81-91). Neither the specification nor the claims set forth any special, non-obvious modifications to the known, conventional software and method steps. A method of using a known method (e.g. population studies) for its known purpose to detect an assocation does not become nonobvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. See *In re Gulack*, 703 F. 2d 1381, 1385 (Fed. Cir. 1983) and MPEP 2106.

Conclusion

13. No claims allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
July 10, 2003

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